Claims

1. Use of at least one proteasome inhibitor for the manufacture of a medicament for the prevention, onset therapy, acute therapy and/or regression of diseases associated with endothelial dysfunction.

2. Use according to claim 1, wherein the diseases associated with endothelial dysfunction are non-insulin related diseases.

3. Use according to claim 1 or 2, wherein the endothelial dysfunction is associated with atherosclerosis, in particular coronary sclerosis and coronary artery disease.

4. Use according to claim 1 or 2, wherein the endothelial dysfunction is associated with heart failure.

5. Use according to claim 1 or 2, wherein the endothelial dysfunction is associated with diseases selected from the group comprising ischemic diseases such as peripheral arterial occlusive disease, e.g. critical leg ischemia, myocardial infarction and ischemic diseases of organs, e.g. of the kidney, spleen, brain, and lung.

6. Use according to any of the foregoing claims 1 or 2, wherein the proteasome inhibitor is selected from a group comprising:

   a) naturally occurring proteasome inhibitors comprising:
   peptide derivatives which have a C-terminal expoxy keton structure, β-lacton-derivatives, aclacinomycin A, lactacystin, clastolactacystein;

   b) synthetic proteasome inhibitors comprising:
   modified peptide aldehydes such as N-carbobenzoxy-L-leucinyl-L-leucinyl-L-leucinal (also referred to as MG132 or zLLL), or the boric acid derivative of MG232, N-carbobenzoxy-Leu-Nva-H (also referred to as MG115), N-acetyl-L-leucinyl-L-leucinyl-L-norleucinal (also referred to as LLnL), N-carbobenzoxy-Ile-Glu(OBut)-Ala-Leu-H (also referred to as PS1);

c) peptides comprising:
an α,β,-epoxyketone-structure, vinyl-sulfones such as, carbobenzoxy-L-leucinyl-L-leucinyl-L-leucin-vinyl-sulfon or, 4-hydroxy-5-iodo-3-nitrophenylacetyl-L-leucinyl-L-leucinyl-L-leucin-vinyl-sulfon (NLVS);

d) Glyoxal- or boric acid residues such as: pyrazyl-CONH(CHPhe)CONH(CHisobutyl)$B(OH)_2$ and dipeptidyl-boric-acid derivatives;

e) Pinacol-esters such as: benzyloxycarbonyl(Cbz)-Leu-leuboro-Leu-pinacol-ester.

7. Use according to any of the foregoing claims, wherein the proteasome inhibitor is selected from a group comprising PS-314 as a peptidyl-boric-acid derivative which is N-pyrazinecarbonyl-L-phenylalanin-L-leucin- boric acid ($C_{19}H_{25}BN_4O_4$); PS-519 as a β-lacton- and a lactacystin-derivative which is 1R-[1S, 4R, 5S] -1-(1-Hydroxy-2methylpropyl)-4-propyl-6-oxa-2azabicyclo[3.2.0]heptane-3,7-dione ($C_{12}H_{19}NO_4$); PS-273 (morpholin-CONH-(CH-naphthyl)-CONH-(CH-isobutyl)-$B(OH)_2$) and its enantiomer; PS-293; PS-296 (8-quinolyl-sulfonyl-CONH-(CH-napthyl)-CONH(-CH-isobutyl)-$B(OH)_2$); PS-303 (NH_2(CH-naphthyl)-CONH-(CH-isobutyl)-$B(OH)_2$; PS-321 as (morpholin-CONH-(CH-naphthyl)-CONH-(CH-phenylalanin)-$B(OH)_2$); PS-334 (CH_3-NH-(CH-naphthyl-CONH-(CH-Isobutyl)-$B(OH)_2$); PS-325 (2-quinol-CONH-(CH-homo-phenylalanin)-CONH-(CH-isobutyl)- $B(OH)_2$; PS-352 (phenyalanin-CH_2-CH_2-CONH-(CH-isobutyl)l-$B(OH)_2$; PS-383 (pyridyl-CONH-(CH_pF-phenylalanin)-CONH-(CH-isobutyl)-$B(OH)_2$); PS-341; and PS-1 Z-Ile-Glu(O*t*Bu)-Ala-Leu-CHO; PS-2 [Benzyloxycarbonyl)-Leu-Leu-phenylalaninal or Z-LLF-CHO or Z-Leu-Leu-Phe-CHO PS-1; PS-519 as a β-lacton- and a lactacystin-derivative which is 1R-[1S, 4R, 5S]-1-(1-Hydroxy-2methylpropyl)-4-propyl-6-oxa-2azabicyclo[3.2.0]heptane-3,7-dione ($C_{12}H_{19}NO_4$); epoxomicin ($C_{28}H_{86}N_4O_7$) and eponemycin ($C_{20}H_{36}N_2O_5$).

8. Use according to any of the foregoing claims, wherein the proteasome inhibitor is selected from a group comprising a peptide aldehyde, a petipde boronate, a peptide vinylsulfone, a peptide epoxyketone, a lactacystin, a peptide α-ketonaldehyde, an α-

ketoamide, an indanonpeptide, a polyalkylenaldehyde, a polyphenol such as cathechin-3-gallate.

9. Use according to any of the foregoing claims, wherein the proteasome inhibitor is selected from a group comprising Z-Leu-Leu-Leu-al (MG132), Z-Ile-Glu(OtBu)-Ala-Leu-al (PS-1), CEP1612, pyrazylcarbonyl-Phe-Leu-boronate (PS-341), dansyl-Phe-Leu-boronate (DFLB), morpholinonaphthylalanin-Leu-boronate (MG273), NIP-Leu_3-vinylsulfone (NLVS), Tyr-Leu_3-VS, NIP-Leu-Leu-Asn-VS, Ada-Tyr-Ahx_3-Leu_3-VS, Ada-Lys(bio)-Ahx_3-Leu_3-VS, Ac(Me)-Ile-Ile-Thr-Leu-EX (epoxomicin), dihydroeponemycin, lactacystin, clasto-lactacystin-beta-lacton (omuralid), PS-519, Ac-Leu-Leu-Nle-al (ALLN), 3,4-dichloroisocoumarin (DCI), 4-(2-aminoethyl)-bezolsulfonylfluorid (pefablock SC), TMC-95-A, gliotoxin, (-)epigallocatechin-3-gallate (EGCG), ritonavir, lovastatin, aclacinomicin A (aclarubicin), cyclosporin, wherein Z represents benzyl oxycarbonyl, all represents aldehyde, VS represents vinylsulfone, NIP represents 3-nitro-4-hydroxy-5-iodophenylacetate, and bio represents biotin.

10. Use according to any of the foregoing claims, wherein the proteasome inhibitor interferes with gene expression of at least one component of the proteasome complex.

11. Use according to claim 10, wherein the proteasome inhibitor interfering with proteasomal gene expression is selected from a group comprising antisense RNA, double stranded RNA and oligonucleotides hybridising with a DNA sequence encoding at least one component of the proteasome complex.

12. Use according to any of claims 10 and 11, wherein the proteasome inhibitor interfering with proteasomal gene expression is selected from a group comprising a knock out construct.

13. Use of at least one proteasome inhibitor for the manufacture of a medicament for the prevention, onset therapy, acute therapy and/or regression of a disease, wherein the proteasome inhibitor dose provided to a patient in need is in the nmol range.

14. Use according to claim 13, wherein the disease is associated with endothelial dysfunction.

15. Use according to claim 13 or 14, wherein the disease associated with endothelial dysfunction is a non-insulin related disease.

16. Use according to any of claims 13-15, wherein the endothelial dysfunction is associated with atherosclerosis, in particular coronary sclerosis and coronary artery disease.

17. Use according to any of claim 13-15, wherein the endothelial dysfunction is associated with heart failure.

18. Use according to any of claim 13-15, wherein the endothelial dysfunction is associated with diseases selected from the group comprising ischemic diseases such as peripheral arterial occlusive disease, e.g. critical leg ischemia, myocardial infarction and ischemic diseases of organs, e.g. of the kidney, spleen, brain, and lung.

19. Use according to any of claims 13-18, wherein the proteasome inhibitor is selected from a group comprising:

a) naturally occurring proteasome inhibitors comprising:
peptide derivatives which have a C-terminal expoxy keton structure, β-lacton-derivatives, aclacinomycin A, lactacystin, clastolactacystein;

b) synthetic proteasome inhibitors comprising:
modified peptide aldehydes such as N-carbobenzoxy-L-leucinyl-L-leucinyl-L-leucinal (also referred to as MG132 or zLLL), or the boric acid derivative of MG232, N-carbobenzoxy-Leu-Nva-H (also referred to as MG115), N-acetyl-L-leucinyl-L-leucinyl-L-norleucinal (also referred to as LLnL), N-carbobenzoxy-Ile-Glu(OBut)-Ala-Leu-H (also referred to as PS-1);

c) peptides comprising:
an α,β,-epoxyketone-structure, vinyl-sulfones such as, carbobenzoxy-L-leucinyl-L-leucinyl-L-leucin-vinyl-sulfon or, 4-hydroxy-5-iodo-3-nitrophenylacetyl-L-leucinyl-L-leucinyl-L-leucin-vinyl-sulfon (NLVS);

d) Glyoxal- or boric acid residues such as: pyrazyl-CONH(CHPhe)CONH(CHisobutyl)$B(OH)_2$ and dipeptidyl-boric-acid derivatives;

e) Pinacol-esters such as: benzyloxycarbonyl(Cbz)-Leu-leuboro-Leu-pinacol-ester.

20. Use according to any of claims 13-19, wherein the proteasome inhibitor is selected from a group comprising PS-314 as a peptidyl-boric-acid derivative which is N-pyrazinecarbonyl-L-phenylalanin-L-leucin- boric acid ($C_{19}H_{25}BN_4O_4$); PS-519 as a β-lacton- and a lactacystin-derivative which is 1R-[1S, 4R, 5S] -1-(1-Hydroxy-2methylpropyl)-4-propyl-6-oxa-2azabicyclo[3.2.0]heptane-3,7-dione ($C_{12}H_{19}NO_4$); PS-273 (morpholin-CONH-(CH-naphthyl)-CONH-(CH-isobutyl)-$B(OH)_2$) and its enantiomer; PS-293; PS-296 (8-quinolyl-sulfonyl-CONH-(CH-napthyl)-CONH(-CH-isobutyl)-$B(OH)_2$); PS-303 (NH_2(CH-naphthyl)-CONH-(CH-isobutyl)-$B(OH)_2$; PS-321 as (morpholin-CONH-(CH-naphthyl)-CONH-(CH-phenylalanin)-$B(OH)_2$); PS-334 (CH_3-NH-(CH-naphthyl-CONH-(CH-Isobutyl)-$B(OH)_2$); PS-325 (2-quinol-CONH-(CH-homo-phenylalanin)-CONH-(CH-isobutyl)- $B(OH)_2$; PS-352 (phenyalanin-CH_2-CH_2-CONH-(CH-isobutyl)l-$B(OH)_2$; PS-383 (pyridyl-CONH-(CH_pF-phenylalanin)-CONH-(CH-isobutyl)-$B(OH)_2$); PS-341; and PS-1 Z-Ile-Glu(O*t*Bu)-Ala-Leu-CHO; PS-2 [Benzyloxycarbonyl)-Leu-Leu-phenylalaninal or Z-LLF-CHO or Z-Leu-Leu-Phe-CHO PS-1; PS-519 as a β-lacton- and a lactacystin-derivative which is 1R-[1S, 4R, 5S]-1-(1-Hydroxy-2methylpropyl)-4-propyl-6-oxa-2azabicyclo[3.2.0]heptane-3,7-dione ($C_{12}H_{19}NO_4$); epoxomicin ($C_{28}H_{86}N_4O_7$) and eponemycin ($C_{20}H_{36}N_2O_5$).

21. Use according to any of claims 13-20, wherein the proteasome inhibitor is selected from a group comprising a peptide aldehyde, a petipde boronate, a peptide vinylsulfone, a peptide epoxyketone, a lactacystin, a peptide α-ketonaldehyde, an α-ketoamide, an indanonpeptide, a polyalkylenaldehyde, a polyphenol such as cathechin-3-gallate.

22. Use according to any of claims 13-21, wherein the proteasome inhibitor is selected from a group comprising Z-Leu-Leu-Leu-al (MG132), Z-Ile-Glu(OtBu)-Ala-Leu-al

(PS-1), CEP1612, pyrazylcarbonyl-Phe-Leu-boronate (PS-341), dansyl-Phe-Leu-boronate (DFLB), morpholinonaphthylalanin-Leu-boronate (MG273), NIP-Leu_3-vinylsulfone (NLVS), Tyr-Leu_3-VS, NIP-Leu-Leu-Asn-VS, Ada-Tyr-Ahx_3-Leu_3-VS, Ada-Lys(bio)-Ahx_3-Leu_3-VS, Ac(Me)-Ile-Ile-Thr-Leu-EX (epoxomicin), dihydroeponemycin, lactacystin, clasto-lactacystin-beta-lacton (omuralid), PS-519, Ac-Leu-Leu-Nle-al (ALLN), 3,4-dichloroisocoumarin (DCI), 4-(2-aminoethyl)-bezolsulfonylfluorid (pefablock SC), TMC-95-A, gliotoxin, (-)epigallocatechin-3-gallate (EGCG), ritonavir, lovastatin, aclacinomicin A (aclarubicin), cyclosporin, wherein Z represents benzyl oxycarbonyl, all represents aldehyde, VS represents vinylsulfone, NIP represents 3-nitro-4-hydroxy-5-iodophenylacetate, and bio represents biotin.

23. Use according to any of claims 13-22, wherein the proteasome inhibitor is MG132.

24. Use according to any of claims 13-23, wherein the proteasome inhibitor interferes with gene expression of at least one component of the proteasome complex.

25. Use according to any of claims 13-24, wherein the proteasome inhibitor interfering with proteasomal gene expression is selected from a group comprising antisense RNA, double stranded RNA and oligonucleotides hybridising with a DNA sequence encoding at least one component of the proteasome complex.

26. Use according to any of claims 13-25, wherein the proteasome inhibitor interfering with proteasomal gene expression is selected from a group comprising a knock out construct.